II. Rejection of Claims Under 35 U.S.C. 112, Second Paragraph

Claims 1, 2, 4-10 and 12-15 have been rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner suggests that the claims read on a non-elected invention. Applicants have amended the claims as discussed *supra* to remove reference to SEQ ID NO: 10 and SEQ ID NO: 11. Withdrawal of this rejection is respectfully requested.

III. Rejection of Claims Under 35 U.S.C. 103(a)

Claims 1, 2, 4-10 and 12-15 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Takekawa et al. (1997) and GenBank Accession No. AF002715, in view of Johnson (US Patent 5,981,265), Johnson (US Patent 6,312,934), Johnson (US Patent 6,333,170), Baracchini et al. (US Patent No. 5,801,154), and Milner et al. (1997). The Examiner suggests it would have been *prima facie* obvious for one of skill to make antisense targeted to MEKK4 based on the sequence taught by Takekawa et al. because the three patents of Johnson teach methods of making antisense to MEKK nucleic acid molecules, including antisense that targets the coding

region of MEKK4 (US Patent No. 6,312,934 B1) and Takekawa et al. disclose that these proteins are involved in similar signaling pathways. Further the Examiner suggests that methods for making antisense to a known gene is well known in the art as taught by Milner et al., while methods for modifying antisense as claimed are taught by Baracchini et al., and methods of inhibiting expression of MEKK4 would be obvious based on what is known in the art. The Examiner further suggests that one of skill would have been motivated to make antisense based on the combination of teaching of Takekawa et al. and the Johnson patents, since antisense was well-known in the art, while Baracchini et al. provides motivation to make antisense in the claimed size range as well as with the claimed modifications. The Examiner suggests that expectation of success is provided by the fact that the sequence of MEKK4 was known in the art and screening for antisense was routine (Milner et al.). Applicants respectfully traverse this rejection.

At the outset, Applicants have amended the claims to refer to targeting specific nucleobase regions within the coding region of MEKK4 with antisense. Support for these amendments to the claims can be found throughout the specification as filed but in particular at pages 79-82.

Takekawa et al. (1997) and GenBank Accession No. AF002715 disclose the sequence of MEKK4 and its role in the JNK pathway. Nowhere does this paper teach or suggest antisense targeted to specific nucleobase regions of MEKK4 (SEQ ID NO: 3) as claimed.

The secondary references cited by the Examiner fail to overcome the deficiencies in teaching of this primary reference.

US Patent 5,981,265 discloses methods for regulating MEKK protein activity by transfecting or transforming a cell with a nucleic acid molecule capable of hybridizing with a nucleic acid molecule consisting of the known MEKK proteins: MEKK1, MEKK2, MEKK3, MEKK4, MEKK5 or MEKK6. Nowhere does this patent teach or suggest that antisense compounds targeted to specific nucleobase regions of these MEKK nucleic acid molecules. It is only with the teaching of the specification in hand that one of skill would understand that certain nucleobase regions of the MEKK4 gene would be successful targets for antisense compounds.

US Patent 6,333,170 B1 discloses the general use of antisense as a tool in conjunction with MEKK proteins. No specific antisense compounds are taught or suggested in this patent, nor are any regions of MEKK4 to be specifically targeted with antisense. Again, it is only with the teaching of the specification in hand that one of skill would understand that certain nucleobase regions

of the MEKK4 gene would be successful targets for antisense compounds.

US Patent 6,312,934 B1 also discloses the general use of antisense as a tool in conjunction with MEKK proteins. Like the other Johnson patents, however, no specific antisense compounds are taught or suggested in this patent. Although the coding region is mentioned generally as a target for antisense, no specific compounds are taught or suggested. Again, it is only with the teaching of the specification in hand that one of skill would understand that certain nucleobase regions of the MEKK4 gene would be successful targets for antisense compounds.

Milner et al. (1997) teaches a general method for screening antisense molecules. However, nowhere does this paper teach or suggest antisense compounds of any size or type targeted to specific regions of MEKK4 nucleic acid molecules as claimed and their use to inhibit gene expression.

Baracchini et al. teaches modifications of antisense oligonucleotides in general. However, nowhere does this reference teach or suggest antisense compounds of any type targeted to specific regions of MEKK4 nucleic acid molecules as claimed.

To establish a *prima facie* case of obviousness, three basic criteria must be met. MPEP 2143. First, there must be some

suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art must teach or suggest all claim limitations. Clearly, the combination of prior art cited fails to teach or suggest the limitations of the amended claims, which claim antisense compounds targeted to specific nucleobase regions of MEKK4 (SEQ ID NO: 3), and methods of inhibiting expression of MEKK4, and thus cannot render the instant claimed invention obvious. Further, there is no suggestion in the references cited to combine the teachings of these references as required under MPEP 2143.01. Accordingly, withdrawal of this rejection is respectfully requested.

IV. Conclusion

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

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Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "**VERSION WITH MARKINGS TO SHOW CHANGES MADE**."

Respectfully submitted,

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Date: **February 19, 2003**

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

Claim 1 has been amended as follows:

1. (thrice amended) A compound 8 to 50 nucleobases in length targeted to ~~5'-untranslated region, a start codon region, a coding region, or a 3'-untranslated region of a nucleic acid molecule encoding MEKK4 of SEQ ID NO: 10,~~ nucleobases 3314 through 3333 of a coding region of a nucleic acid molecule encoding MEKK4 of SEQ ID NO: 3, ~~or an exon region of a nucleic acid molecule encoding MEKK4 of SEQ ID NO: 11 ,~~ wherein said compound specifically hybridizes with ~~one of~~ said regions and inhibits the expression of MEKK4.